OBJECTIONS/REJECTIONS

Objections to the Specification

The Office Action objects to the specification as allegedly "confusing concerning porphyrin content throughout the examples presented." *See* Office Action, page 6, lines 9-10. More specifically, the Office Action states that "Example 1 describes that no porphyrin compound (haemin) is found in the supernatant while 41 ppm porphyrin compound (haemin) is found in the cellular pellet...However, in later examples with identically treated cells, porphyrin compound (cytochrome d) is identified in the supernatant at 13 ppm. Thus, it is confusing how the first analysis identifies no porphyrin compound (haemin) in the supernatant while later analysis does find porphyrin (cytochrome d) in the supernatant." *See* Office Action, page 6, lines 9-10.

Applicants respectfully disagree and traverse this objection to the specification.

Applicants assayed for the presence and quantification of cytochromes in Example 2 of the instant application. In order to conduct this assay, Applicants relied on modified teachings of Winstedt *et al* (Winstedt *et al.*, 182:3863-3866 (2000) a copy of which was provided in the Information Disclosure Statement filed June 19, 2001) which teaches the preparation of membranes from *Enterococcus faecalis*. *See* Winstedt *et al*, page 3863 (2000). Following lysis of the cells via French Press, membrane components harboring cytochromes were liberated into the supernatant. As a result, Applicants assayed and detected membrane-associated cytochromes in the supernatant. By contrast, Applicants relied on a Formic acid-based protocol for the detection of haemin in cellular debris of Example 1. As can be seen, the confusion is an artifact of the protocols for sample preparation.

Therefore, there is no confusion or discrepancy in the teachings of the specification between Examples 1 and 2. Applicants respectfully request reconsideration and withdrawal of the objection to the specification.

Objections to the Claims

Claim 14 was objected to for having improper punctuation. Applicants respectfully disagree with this assertion, and note that the location of the comma provides that the

composition may be in the form of either a frozen composition, a liquid composition or a freeze-dried composition. Accordingly, Applicants request reconsideration and withdrawal of the objection to claim 14 in light of these remarks.

Claim Rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 1, 4-17 and 34-52 were rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for lactic acid bacterial cells modified to contain at least 0.1 ppm haemin," allegedly "does not reasonably provide enablement for lactic acid bacterial cells modified to contain at least 0.1 ppm of ***any*** **porphyrin** containing compound." *See* Office Action, page 8, lines 13-15.

Applicants respectfully disagree and traverse this rejection.

As noted in the Office Action, the enablement requirement requires that the specification enable a person skilled in the art to which the specification pertains, or with which it is most nearly connected, to make and use the claimed invention without undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Factors to consider in determining undue experimentation include (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See* M.P.E.P. § 2164.01(a). However,

> [c]ompliance with the requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed...The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. But because only an enabling disclosure is required, applicant need not describe all actual embodiments.

M.P.E.P. § 2164.02.

Based on the foregoing, Applicants respectfully submit that the specification considered in its entirety including the examples, provides adequate disclosure to enable the scope of the claimed invention. For example, the two working examples found in the specification provide a teaching of the general methodologies necessary for one of skill in the art to practice the claimed invention and to ascertain whether the claimed invention has been produced.

During the interview conducted on December 18, 2003, the Examiner asked Applicants' representatives to explain whether haeme and cytochrome d are the same compounds. Applicants' representatives indicated that they would discuss with Applicants whether haeme and cytochrome d are the same compounds. Applicants have stated that haeme and cytochrome d are indeed different compounds, and are detected in different sample fractions.

The specification also provides a recitation of numerous porphyrin-containing compounds, other than haemin, associated with the invention. For example, the specification provides a description in the working examples of at least one separate porphyrin-containing compound. More specifically, Figure 6 corresponding to Example 1 demonstrates the presence of cytochrome c, which is a distinct compound from haeme (cytochrome c and haeme having different weights as measured by HPLC). Applicants need not provide working examples for the full scope of each and every claim limitation provided that one of skill in the art is enabled to make and use the scope of the claimed invention.

In addition to the teachings of Applicants' specification and working examples, the art provides a degree of predictability regarding the use of porphyrin-containing compounds. The teachings of Zerr *et al* (Oral Microbiol Immunol., 15:365-370 (2000)) and Leung *et al* (FEMS Microbiol Lett., 209:15-21 (2002)) teach the use of a varying array of porphyrin-containing compounds and the effects of these porphyrin-containing compounds on the growth of *Porphyromonas* and *Prevotella* bacterial species. (Copies of Zerr *et al* and Leung *et al* are provided with the Third Supplemental Information Disclosure Statement submitted herewith). For example, Leung *et al* demonstrate that protoporphyrin IX or protoporphyrin-zinc "either in the presence of supplements, $FeCl_2$ or $FeCl_3$ (final concentration, 200 μM), or in the absence of iron supplements, were capable of supporting the growth of hemin-iron restricted *P. intermedia*

to an extent that was comparable to that of the hemin control..." *See* Leung *et al.*, p. 19 (2002). Similarly, Zerr *et al* demonstrated that the addition of various porphyrin-containing compounds induced the growth of *Porphyromonas* species in a liquid culture. The results obtained by Zerr et al, while not achieving equivalent rates of growth over the duration of 120 hours of culture time, did demonstrate that the administration of porphyrin-containing compounds resulted in equivalent cell densities (measured in O.D.) following 120 hours of liquid culturing. *See* Leung *et al.*, Figures 1A and 1B and pages 367-368 (2000).

The above-cited references demonstrate that there is a degree of predictability in the use and administration of a range of porphyrin-containing compounds to various liquid bacterial cell cultures. This art further supports Applicants' assertions that the specification and the working examples, in conjunction with the prior art, enable one of ordinary skill in the art to make and use the full scope of the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 4-17 and 34-52 under 35 U.S.C. §112, first paragraph, as allegedly failing to reasonably provide enablement for lactic acid bacterial cells modified to contain at least 0.1 ppm of any porphyrin containing compound.

Similarly, claims 5, 8-9, 12, 16, 40-42, and 45-52 were rejected under 35 U.S.C. § 112, 1st paragraph as the specification allegedly fails to provide enabling disclosure for the scope of each of these numerous dependent claims. All enablement rejections of these claims were generally premised on the assertions that, while working examples provide enablement for a certain scope of rejected limitation, they do not provide enablement for the claimed scope of that limitation (which is different from the scope of the limitation in the examples). Alternatively, some rejections were based on an assertion that working examples provided enablement for one type of a porphyrin compound, but the specification did not provide enablement for all porphyrin compounds. Applicants respectfully traverse these rejections. Applicants have provided a discussion *supra* of the requirements of an enabling disclosure which do not hinge on the presence of working examples, as well as providing evidence that porphyrin-containing compounds have a degree of predictability in the art. Based on this previous discussion,

Applicants submit that the specification as filed, in view of the state of the art, provides enabling disclosure for the entire claimed subject matter of claims 5, 8-9, 12, 16, 40-42, and 45-52. In particular, the specification (aside from the examples) contains the disclosure of each of the rejected limitations and working examples with a different scope of the rejected limitations than in the specification. The cited articles establish knowledge in the art of common properties between different porphyrin compounds, thereby providing evidence of predictability of various properties of different porphyrin compounds. One of ordinary skill in the art, would have been able to carry out the invention of each rejected claim without undue experimentation based on the combination of: (1) Applicants' disclosure, including the specification and working examples; and (2) state of the art establishing similarity between different porphyrin compounds. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5, 8-9, 12, 16, 40-42, and 45-52 under 35 U.S.C. § 112, 1st paragraph as the specification allegedly fails to provide enabling disclosure.

Claim 11 was rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for lactic acid bacterial cells modified to reduce NOX activity by at least 10% with treatment under aerobic conditions, allegedly does not reasonably provide enablement for lactic acid bacterial cells modified when fermented under anaerobic conditions.

Applicants have amended claim 11 herein to more particularly recite the subject matter sought to be claimed in claim 11. Applicants believe that they have addressed the Examiner's concerns regarding the rejection of claim 11, and request reconsideration and withdrawal of the rejection of claim 11 under 35 U.S.C. § 112, first paragraph.

Claim 34 was rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Office Action, "[t]o enable the instant claims by enabling the deposit of DSM 12015, the record must also contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (*See* M.P.E.P. § 2404.01)."

Applicants have provided herein a facsimile of a Declaration of Deposit, wherein it is declared that strain CHCC373, deposited under the terms of the Budapest treaty and assigned accession number DSM 12015 by DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, will be irrevocably and without restriction or condition made available to the public upon the granting of the patent. Accordingly, it is believed that the Examiner's concerns have been addressed by way of submission of the Declaration of Deposit, and Applicants respectfully request reconsideration and withdrawal of the rejection of claim 34 under 35 U.S.C. § 112, 2nd paragraph.

Claim Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 8 and 9 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite in the recitation of the term "about." According to the Office Action, the term "about" lacks clarity.

Applicants respectfully disagree and traverse this rejection.

According to the CCPA, "it is well established that 'claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest *reasonable* interpretation.'" In re Marosi, 710 F.2d 799, 802, 218 USPQ (BNA) 289, 292 (Fed. Cir. 1983) (*quoting* In re Okuzawa, 537 F.2d 545, 548, 190 USPQ (BNA) 464, 466 (CCPA 1976)).

"Definiteness problems often arise when words of degree are used in a claim. That some claim language may not be precise, however, does not automatically render a claim invalid." Seattle Box v Indus. Crating and Packing, 731 F.2d 818, 826, 221 USPQ 568, 573-574 (Fed. Cir. 1984). Regarding issues of definiteness of claim language, "the question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification." BJ Services v. Halliburton Energy Services, 338 F.3d 1368, 67 USPQ2d (BNA) 1692 (Fed. Cir. 2003) ("about" in claim does not render the claim indefinite in view of all the evidence, including the specification, in this case).

The term "about", as used in claim 8, is a term of degree. While not definite, Applicants assert that one of skill in the art reading the claim language and the specification in its entirety

would understand that the claim recitation of "...about two hours..." includes a reasonable degree of time duration either greater than or less than two hours, but substantially two hours in length. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 8 and 9 under 35 U.S.C. § 112, 2nd paragraph for the allegedly indefinite recitation of "about."

Claim 34 was rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. More specifically, the Office Action asserts that the term "bacterial species" does not have proper antecedent basis in Claim 1, and clarification is requested.

Applicants respectfully traverse this rejection. Claim 34 depends from claim 6, which provides antecedent basis for "bacterial species." Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 34 under 35 U.S.C. § 112, 2nd paragraph.

Claims Rejections under 35 U.S.C. § 103

Claims 1, 4-7, 10-17, 35-39, 43, 44, 48 and 49 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,075,226 to Kaneko *et al.* (hereinafter "Kaneko"). More specifically, the Office Action states that the rejected claims are rendered obvious in light of the teachings of Kaneko, as allegedly "[i]t would have been obvious to one of ordinary skill in the art to produce the claimed cells because said cells are within the scope of the claimed invention of Kaneko (USPN 5,075,226). One would have been motivated to practice the full scope of the invention of Kaneko et al (USPN 5,075,226) for the purpose of effectively producing diacetyl and acetoin, which are commercially useful flavoring agents." *See* Office Action, page 20, lines 5-9. "All other limitations in the instant claims are inherent based on the treatment with 10 mg/L haemin that is disclosed in the examples of the instant specification." *See* Office Action, page 19, lines 17-19.

Applicants respectfully disagree and traverse this rejection.

As an initial matter, Applicants respectfully disagree that the teachings of Kaneko inherently provide the claimed invention. Under the doctrine of inherency, if an element is not

expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element "is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill...Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." Rosco Inc. v. Mirror Lite Co., 64 USPQ2d 1676, 1680-81 (Fed. Cir. 2002). In the instant case, the working examples of Kaneko provide the administration of hemin at concentrations ranging from approximately 0.3 to approximately 2.8 mg/L, at least one order of magnitude lower than in Applicants' working examples (i.e., 10 mg/L). There is no basis for asserting from the teachings of Kaneko that the Applicants' claimed invention will inherently result in Kaneko's examples, given at least that difference in experimental protocols. Thus, one of ordinary skill in the art could not recognize the Applicant's claimed invention from the teachings of Kaneko, given the differences in experimental protocols.

> In order to establish a *prima facie* case of obviousness, three basic criteria must be met.
>
> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

M.P.E.P. § 2142.

Applicants respectfully assert that the Kaneko reference fails to provide an expectation of achieving a modified lactic acid bacterial cell that has been treated with a porphyrin-containing substrate to cause the cell to contain at least 0.1 ppm on a dry matter basis of a porphyrin compound at least because there is no evidence that such a cell is inherently produced in any of Kaneko's examples, nor that a person of ordinary skill in the art would expect to obtain it. Such a person would expect to obtain diacetyl and acetoin which are the products of Kaneko's method. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 4-7, 10-17, 35-39, 43, 44, 48 and 49 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,075,226 to Kaneko *et al.*

REQUEST FOR ALLOWANCE

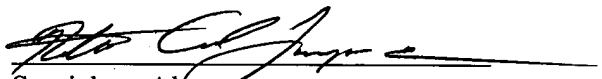
An indication of allowance of all claims is solicited. In the event any issues are outstanding, Applicants would appreciate the courtesy of a telephone call to the undersigned counsel to resolve such issues in an expeditious manner and place the application in condition for allowance.

It is believed that all necessary fees are enclosed. However, if any additional fees are determined to be due, the Commissioner is hereby authorized to charge these fees to the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: February 2, 2004

By: 

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